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Synthesis of 3-phenylnaphthalenic derivatives as new selective MT_2 melatoninergic ligands

Sophie Poissonnier-Durieux [a], Mohamed Ettaoussi [a], Basile Pérès [a], Jean A. Boutin [b], Valérie Audinot [b], Caroline Bennejean [c], Philippe Delagrange [c], Daniel Henri Caignard [c], Pierre Renard [c], Pascal Berthelot [a], Daniel Lesieur [a], Saïd Yous [a,*]

[a] Faculté de Pharmacie, Laboratoire de Chimie Thérapeutique (EA 1043), 3 rue du Professeur Laguesse, BP 83, 59006 Lille Cedex, France
[b] Division de Pharmacologie Moléculaire et Cellulaire, Institut de Recherches Servier, 125 Chemin de Ronde, 78290 Croissy-sur-Seine, France
[c] Institut de Recherches Internationales Servier, 6 Place des Pléiades, 92415 Courbevoie Cedex, France

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ABSTRACT

A series of naphthalenic analogues of melatonin were prepared and evaluated as melatonin receptor MT_2 selective ligands. Activity and MT_2 selectivity can be modulated with suitable variations of the C-3 phenyl and the acyl group on the C-1 side chain. Surprisingly, in contrast with what had been previously described in other series (2-benzylindoles, 2-benzylbenzofurans and 3-phenyltetralins), the presence of a C-3 phenyl with a functional group on the meta position seems to be primordial for MT_2 affinity and selectivity. Indeed, *N*-[2-(3-(3-hydroxymethylphenyl)-7-methoxynaphth-1-yl)ethyl]acetamide (**21**) is one of the best MT_2 selective ligands described until now and behaves as an antagonist.

1. Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine, MLT) is synthesized and released by the pineal gland in a circadian fashion, with high levels occurring during the night. Indeed its synthesis is regulated by the day–night alternance and by the way MLT transmits to the organism information about the photoperiod.[1] This pineal neurohormone regulates and modulates a myriad of physiological functions including, in mammals, the control of seasonal reproduction,[2] circadian adjustments,[3] immunoresponsiveness[4] and vascular regulation,[5] among others. The diversity of MLT's response within the body may be attributed to the fact that its receptors are expressed in a wide variety of tissues.[6–13] To date, two mammalian MLT receptors have been cloned (MT_1 and MT_2).[2,3,7,8] Both are G-protein coupled receptors.[14] Recently another MLT binding site (MT_3)[15] has been described in hamster as homologue of the cytoplasmic quinone reductase 2[16] (see Charts 1 and 2).

The physiological significance of MT_1, MT_2 and MT_3 subtypes can be ascertained with the continual development of specific and selective affinity ligands. As more knowledge is gained about these receptors, their importance as therapeutic targets in pathophysiological states will increase.

Many series of MLT receptor agonists have been reported. Some of these MLT receptor agonist ligands are currently under clinical evaluation or have been approved for their sleep inducing properties or for circadian phase shift action. Agomelatine[17] characterized as an MT_1/MT_2 agonist and 5-HT_{2C} antagonist[18] is in registration for depression. Ramelteon is at present the only melatonin receptor agonist marketed for the treatment of insomnia,[19] and other ligands such as LY 156735[20] have been tested in clinical trials for their hypnotic properties.

Recently receptor subtype selectivity has registered some important advances leading to the identification of a small number of selective compounds.[21a,b] While only few examples of MT_1 selective antagonists are reported,[22] several series of MT_2[23–34] or MT_3 ligands have been described and are competitive agonists or antagonists with varying degrees of selectivity.[35–37] MT_2 receptor selective ligands belong to various structural classes displaying different degrees of binding affinity and selectivity; they comprise benzofuran[28] and tetrahydronaphtalenic derivatives,[29] 6,7-dihydro-5*H*-benzo[*c*]azepino[2,1-*a*]indoles,[25] 2-*N*-acylaminoalkylindoles,[24] and tetrahydroisoquinoline derivatives.[38] Luzindole, the first competitive MLT receptor antagonist discovered, shows higher affinity for the MT_2 than for the MT_1 subtype.[39] This compound was first used to demonstrate the presence of MT_2 receptors mediating inhibition of dopamine release in rabbit retina and phase shift of circadian rhythms in the rodent biological clock [the suprachiasmatic nucleus (SCN)].[3] Like luzindole, other MT_2

* Corresponding author. Tel./fax: +33 (0)320964375.
E-mail address: said.yous@univ-lille2.fr (S. Yous).

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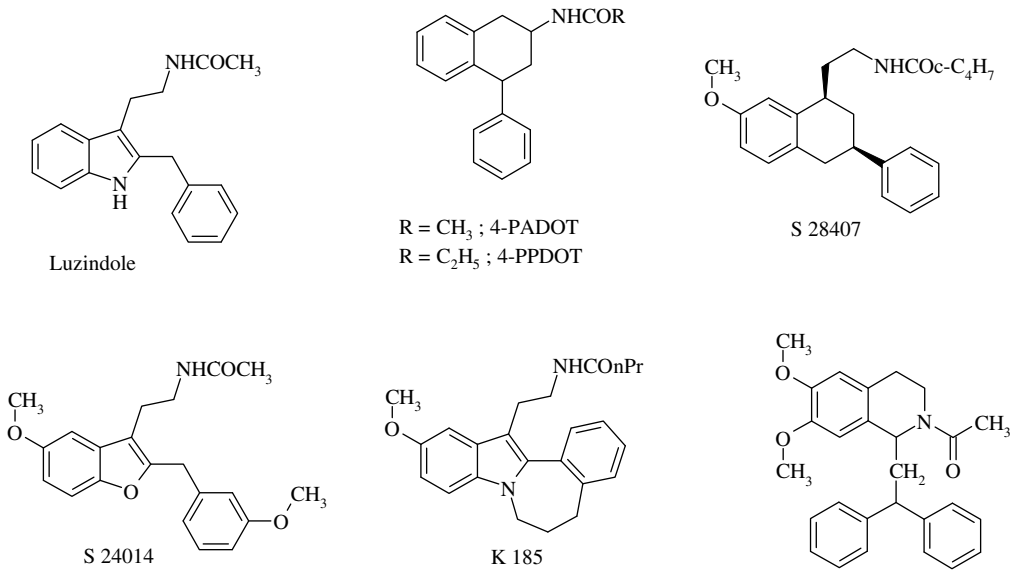


Chart 1. Chemical structures of MT_2-selective antagonists and partial agonists.

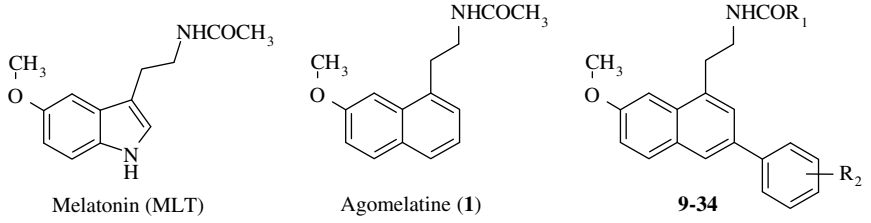


Chart 2. Chemical structures of MLT, agomelatine (**1**) and general structure of compounds **9**–**34**.

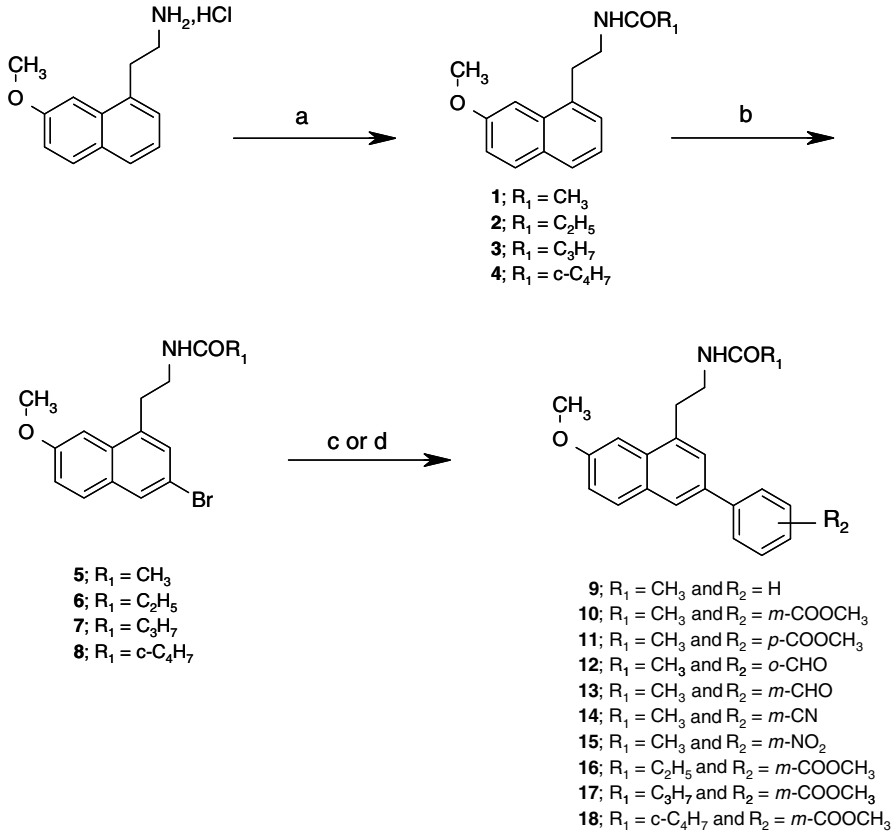
selective antagonists including 4-phenyl-2-acylaminotetralins[39] are structurally characterized by the presence of a phenyl or a benzyl group on the nucleus bearing the 3-alkylamido side chain.[40] Therefore, along this line of thought and expanding on what had been already reported, we first developed a new series of *N*-[2-(2-arylalkylbenzofuran-3-yl)ethylamide.[28] The presence of a lipophilic substituent out of the plane of the aromatic nucleus is a common and consistent structural motif found in most of these MLT ligands, and with others, we have hypothesized that this arrangement was the key feature for MT_2 selectivity.[23,25,28,30]

In this paper we present a novel series of 3-phenylnaphthalenic derivatives as MT_2 selective ligands. In a previous work, we introduced a phenyl substituent in the C-3 position (**9**)[41] of the naphthalenic bioisoster of MLT (agomelatine, **1**).[17] To investigate in detail the influence of structural variations on both affinity and selectivity (C-3 phenyl group substitution, length of the side chain, nature of the acyl group, etc.), the synthesis of additional compounds (**10**, **13** and **19**–**34**) has been performed. For all these compounds, the synthesis, the binding data (human MT_1 and MT_2), and some activity results for the human MT_2 receptors are reported.

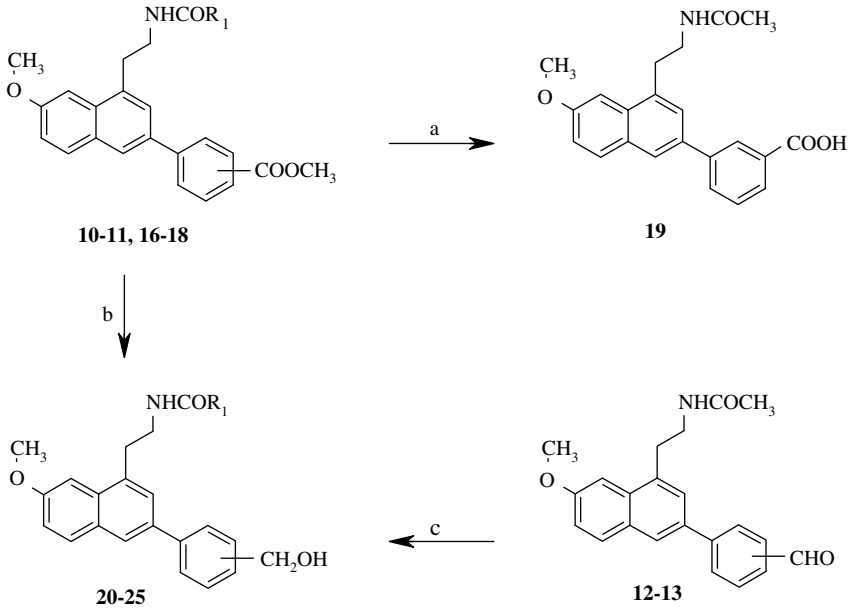
2. Results and discussion

2.1. Chemistry

The syntheses of 3-aryl naphthalene derivatives have been accomplished as described in Schemes 1–3. Introduction of aryl substituents on the 3-position of the heterocycle was carried out by three steps (Scheme 1). Starting from 2-(7-methoxynaphth-1-yl)ethylamine hydrochloride,[17] *N*-acylated derivatives **1**–**4** were first prepared as previously reported by some of us[42] according to a variant of the Schotten–Baumann reaction[43] by treatment in a biphasic medium with the appropriate acid chlorides in the presence of potassium carbonate as base. Subsequently, bromination of compounds **1**–**4** using bromine in acetic acid[44] led to the 3-bromo derivatives **5**–**8** which were reacted under Suzuki conditions in the presence of the appropriate aryl boronic acids and palladium acetate (method A) or triphenylphosphine palladium (method B)[45] to afford compounds **9**–**18**. Saponification of the methyl ester **10** with aqueous sodium hydroxide gave access to the corresponding carboxylic acid **19** (Scheme 2). Alcohols **20**–**25** were obtained either from the corresponding esters by treatment with lithium aluminum hydride in THF and diethyl ether (method A) or from aldehydes **12**–**13** by treatment with sodium borohydride in methanol (method B). Treatment of **21** with 45% HBr in acetic acid[46] led to **26**, which was reacted either with sodium iodide[47] to give **27** or with sodium methoxide[48] to afford **28** (Scheme 3). Catalytic hydrogenation of the cyano group of **14** and of the nitro group of **15** to the corresponding amines **29** and **30** was performed over Raney nickel and 10% palladium on charcoal, respectively. Acetamide **34** was generated from amine **30** by action of acetyl chloride and potassium carbonate in a biphasic medium. Attempts to achieve N-methylation of **30** with formaldehyde and sodium cyanoborohydride were unsuccessful due to the formation of the *N*,*N*-dimethylamine **33** as the major reaction product. Treatment of **30** with ethyl chloroformate and DIPEA provided carbamate **31**. Unfortunately, attempts to reduce **31** with lithium aluminum hydride did not give access to *N*-methylamine **32**. The final strategy em-



Scheme 1. Synthesis of Compounds **1**–**18**. Reagents: (a) R_1COCl, K_2CO_3, methylene chloride, water; (b) Br_2, acetic acid; (c) $R_2C_6H_4B(OH)_2$, $Pd(OCOCH_3)_2$, $NaHCO_3$, $Br^+N^-(C_4H_9)_4$, dioxane, water (method A); (d) $R_2C_6H_4B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene, water, ethanol (method B).

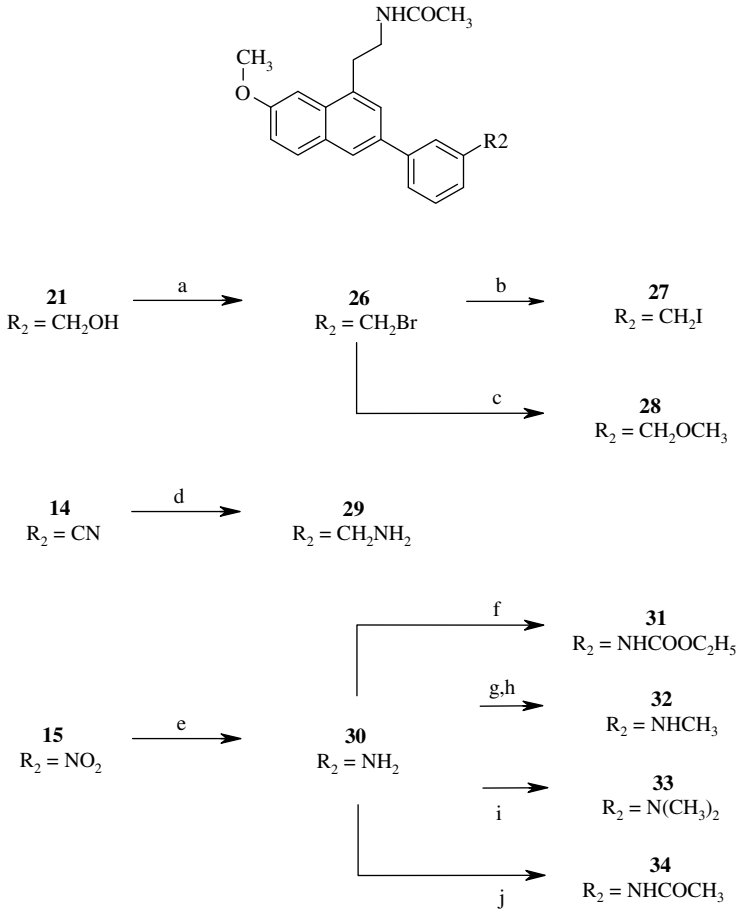


Scheme 2. Synthesis of Compounds **19**–**25**. Reagents: (a) NaOH, methanol, water; (b) $LiAlH_4$, ether, tetrahydrofuran (method A); (c) $NaBH_4$, methanol (method B).

ployed a two-step reaction sequence involving treatment with ethyl orthoformate followed by reduction with sodium borohydride and provided the desired *N*-methylamine **32** as the only product.

2.2. Pharmacology

The chemical structures, binding affinities and MT_1/MT_2 selectivity ratios of the new compounds are reported in Table 1. These



Scheme 3. Synthesis of Compounds **26**–**34**. Reagents: (a) 45% HBr–AcOH; (b) NaI, acetone; (c) CH_3ONa, methanol; (d) H_2, Raney nickel, ethanol; (e) H_2, Pd/C, methanol; (f) $ClCOOC_2H_5$, DIPEA, THF; (g) TFA, $HC(OC_2H_5)_3$; (h) $NaBH_4$, ethanol; (i) 37% HCHO, $NaBH_3CN$, acetonitrile; (j) CH_3COCl, K_2CO_3, methylene chloride, water.

compounds were evaluated for their binding affinity for human MT_1 and MT_2 receptors stably transfected in Human Embryonic Kidney (HEK 293) cells or Chinese Hamster Ovarian (CHO) cells, using 2-[^{125}I]iodomelatonin as radioligand.[41] At each receptor, binding affinities were verified for more than fifty selective and non-selective molecules, either using the transfected HEK 293 or the CHO cell lines. The correlations between affinities in HEK 293 and CHO cells are highly significant ($r = 0.98$), for both MT_1 and MT_2 receptors. This high correlation allows the comparison of the affinities on the receptors expressed in two different cell types and to draw structure–activity relationships.

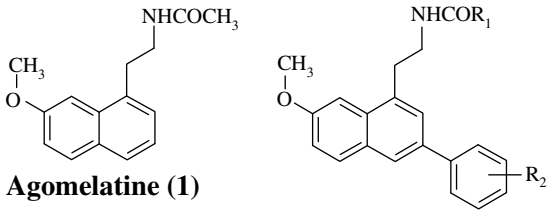
The intrinsic activity of the most interesting compounds (selectivity ratio higher than 50 and K_i lower than 10 nM) has been evaluated only on the MT_2 receptor subtype, due to the weak affinity for the MT_1 subtype. The results are shown in Table 2. The [^{35}S]GTPγS binding assay used to determine the functional activity of the compounds was performed using Chinese Hamster Ovarian (CHO) cell lines stably expressing the human MT_2 receptors.

Introduction of a phenyl substituent in the C-3 position of the naphthalene ring of agomelatine causes a 140-fold decrease in the MT_1 but maintains the MT_2 binding affinity, leading to a variation of the MT_1/MT_2 selectivity ratio from 0.2 to 132 (**9**).[41] These results are in agreement with what is reported in previous studies[24]: a hypothesis on selective binding to the MT_2 receptor is based on the presence of an additional pocket at the MT_2 receptor, positioned out of the plane of the aromatic nucleus that characterises MLT receptor ligands. Contrary to 2-benzylindoles, 2-benzylbenzofurans and 3-phenyltetralins, the 3-phenyl ring of compound **9** is not out of the plane of the naphthalene nucleus. We can therefore assume either that the additional pocket is wider than previously described or that, in this case, the naphthalene ring is accommodated within the receptor in a different way than that of the other aromatic nuclei. On the other hand, compound **9** acts as a partial MT_2 agonist. We therefore selected this compound as a lead to investigate structure–affinity (selectivity) and structure–activity relationships for MT_1 and MT_2 subtypes.

(i) We first introduce a hydroxymethyl group on the various positions of the C-3 phenyl ring, the choice of this substituent being justified by its hydrophilic character and its H-bond donor and acceptor capability. The results obtained show that MT_2 affinity and selectivity strongly depend on the position of this group on the phenyl ring, the meta regioisomer (**21**) being the most favourable: compound **21** (MT_1/MT_2 ratio 763) is about sixfold more selective than the lead **9** and, respectively, 250- and 50-fold more selective than its ortho and para isomers. Moreover, this compound presents an affinity for MT_2 similar to that of MLT and acts as an MT_2 antagonist.

(ii) In the tetrahydronaphthalenic series, variations of the acyl group on the C-1 side chain had shown that acetyl was not the optimum group for selectivity, the best results being obtained with the bulkier cyclobutyl.[29] We then replace the methyl group of the acetamido side chain of **21** by homologous alkyl and cycloalkyls. Surprisingly the results are opposite to those obtained in the tetralinic series: the cyclobutyl derivative **25** shows the worst MT_2 affinity (48 nM) and MT_1/MT_2 selectivity ratio (31), whereas the two alkyl homologous **23**–**24** retain good MT_2 affinities (0.52 and 0.28 nM, respectively) and a threefold lower selectivity than the acetyl one (**21**) which remains the best compound.

Table 1
MT_1 and MT_2 receptor binding affinities of 3-phenylnaphthalene compounds



Agomelatine (1)

Compound	R_1	R_2	K_i ± SEM (nM) MT_1	K_i ± SEM (nM) MT_2	MT_1/MT_2
MLT	—	—	0.14 ± 0.03	0.41 ± 0.04	0.3
Agomelatine	—	—	0.06 ± 0.01	0.27 ± 0.04	0.2
9	CH_3	H	53.0 ± 12	0.37 ± 0.05	132
20	CH_3	*o*-CH_2OH	5.90 ± 0.12	1.86 ± 0.03	3
21	CH_3	*m*-CH_2OH	275 ± 79.5	0.36 ± 0.02	763
22	CH_3	*p*-CH_2OH	297 ± 21.5	23.0 ± 5.70	14
23	C_2H_5	*m*-CH_2OH	125 ± 10.3	0.52 ± 0.06	240
24	C_3H_7	*m*-CH_2OH	60.3 ± 7.10	0.28 ± 0.03	215
25	c-C_4H_7	*m*-CH_2OH	1510 ± 277	48.3 ± 1.91	31
28	CH_3	*m*-CH_2OCH_3	204 ± 2.03	0.95 ± 0.09	214
13	CH_3	*m*-CHO	137 ± 0.17	0.42 ± 0.003	326
10	CH_3	*m*-$COOCH_3$	24.7 ± 10.9	0.64 ± 0.18	39
19	CH_3	*m*-COOH	3830 ± 1130	43.3 ± 12.5	89
26	CH_3	*m*-CH_2Br	50.7 ± 1.33	0.56 ± 0.16	91
27	CH_3	*m*-CH_2I	126 ± 28.4	0.71 ± 0.11	178
29	CH_3	*m*-CH_2NH_2	1390 ± 100	3.40 ± 0.32	409
30	CH_3	*m*-NH_2	82 ± 23	0.27 ± 0.04	304
32	CH_3	*m*-$NHCH_3$	82.5 ± 0.50	0.51 ± 0.01	162
33	CH_3	*m*-$N(CH_3)_2$	49.8 ± 2.10	0.94 ± 0.29	53
31	CH_3	*m*-$NHCOOC_2H_5$	124 ± 7.52	8.30 ± 0.50	15
34	CH_3	*m*-$NHCOCH_3$	38.4 ± 4.39	7.54 ± 2.67	5

Concentration–response curves were analyzed by non-linear regression comparing a one-site and a two sites analysis. All the curves were found to be monophasic with a Hill number close to unity (not shown). Binding affinities (nM) are expressed as mean K_i ± SEM of at least three independent experiments. The selectivity ratio between MT_1 and MT_2 receptors is calculated for each compound.

Table 2
Intrinsic activity values

Compound	MT_2			
	EC_{50} ± SEM (nM)	E_{max} ± SEM (%)	Kb ± SEM (nM)	I_{max} ± SEM (%)
MLT	0.49 ± 0.05	100	nd	nd
Agomelatine (**1**)	0.1 ± 0.04	91 ± 7	nd	nd
9	2.4 ± 0.8	56 ± 6	nd	nd
21	0.76 ± 0.4	23 ± 1	0.8 ± 0.5	95.5 ± 0.5
13	1.3 ± 0.02	45 ± 2.6	1 ± 0.3	61.5 ± 13.6
23	0.7 ± 0.2	45.7 ± 1.4	0.7 ± 0.3	54.3 ± 10.6
24	0.6 ± 0.03	51 ± 4.7	2.2 ± 1.9	51.5 ± 8.5
26	1 ± 0.2	32.3 ± 5.8	0.8 ± 0.1	72.5 ± 7.5
27	nc	<10	4.1 ± 1.8	89 ± 9
28	13.3 ± 8	32.5 ± 7	1.7 ± 0.8	77 ± 8
29	nc	<10	8.7 ± 1.9	87 ± 5
30	1.3 ± 0.2	41 ± 4	0.8 ± 0.3	37 ± 0
32	0.5 ± 0.2	47.2 ± 3	0.9 ± 0.4	72 ± 1
33	1.5 ± 0.5	30 ± 5	1.3 ± 0.3	87 ± 17

Concentration–response curves were analyzed by non-linear regression. Agonist potency was expressed as EC_{50} ± SEM (nM) while the maximal efficacy, E_{max} ± SEM was expressed as a percentage of that observed with melatonin 1 μM (=100%). Antagonist potency to inhibit the effect of melatonin (30 or 3 nM, respectively, for MT_1 and MT_2 receptors) was expressed as KB ± SEM I_{max} (maximal inhibitory effect) was expressed as a percentage of that observed with melatonin at 3 nM for MT_2 receptor. Data are mean of at least three independent experiments.
nd: not determined; nc: not calculated.

(iii) Starting from **21**, it was therefore interesting to substitute the hydroxymethyl with other functional groups aiming at varying lipophilic, electronic and/or steric parameters.

(a) *Methylether:* Substitution of the alcoholic function for the corresponding methylether (**28**) leads to a threefold lower MT_2 affinity with a slightly higher MT_1 affinity. The selectivity ratio (MT_1/MT_2 = 214), being near that of the unsubstituted compound (**9**).

(b) Carbonyl derivatives: Replacing the hydroxymethyl group by a carboxaldehyde (**13**) results in preservation of MT_2 and a twofold increase of MT_1 affinity. This explains the good and slightly reduced selectivity ratio (MT_1/MT_2 = 326). Compound **13** is one of the best in this series contrary to the other carbonyl derivatives: the methylester **10** shows a twofold lower affinity on the MT_2 subtype but a 10-fold higher on the MT_1, whereas the corresponding carboxylic acid (**19**) has a strongly reduced affinity on both MT_1 (3830 nM) and MT_2 (43.3 nM) subtypes. The selectivity ratios of these compounds are low (39 and 89, respectively).

(c) Halomethyl derivatives: The bromomethyl (**26**) and iodomethyl (**27**) derivatives possess a similar binding profile with the same degree of MT_2 affinity as **21** and a two- to fivefold higher affinity for the MT_1 subtype, the respective selectivity ratios being 91–178.

(d) Nitrogen derivatives: The bioisosteric replacement of the hydroxyl group of **21** by a primary amine leads to noticeable but quite similar loss of MT_1 and MT_2 binding affinities. Nevertheless, the resulting compound **29** retains a good MT_2 affinity (3.4 nM) and one of the best MT_1/MT_2 selectivity ratio (409). The corresponding aromatic primary amine (**30**)[41] that comes from deletion of the methylene bridge has the same MT_2 affinity as **21** and only a threefold higher MT_1 affinity leading to a

Table 3
Elemental analyses

Compound	% C		% H		% N	
	Calcd	Found	Calcd	Found	Calcd	Found
9	86.92	86.87	7.29	7.32	5.79	5.83
10	73.19	72.88	6.14	6.17	3.71	3.69
11	73.19	73.22	6.14	6.08	3.71	3.63
13	76.06	75.76	6.09	6.10	4.03	4.01
14	76.72	76.65	5.85	5.99	8.13	7.76
16	73.64	73.70	6.44	6.44	3.58	3.58
17	74.05	73.93	6.71	6.77	3.45	3.64
18	74.80	74.55	6.52	6.48	3.35	3.32
19	72.71	72.46	5.82	5.76	3.85	3.86
20	75.62	75.76	6.63	6.40	4.01	4.01
21	75.62	75.33	6.63	6.61	4.01	4.22
22	75.62	75.44	6.63	6.71	4.01	3.86
23	76.01	75.81	6.93	6.98	3.85	3.80
24	76.36	76.21	7.21	7.15	3.71	3.72
25	77.09	76.98	6.99	7.05	3.60	3.53
26	64.09	63.92	5.38	5.37	3.40	3.42
27	57.53	57.53	4.83	4.83	3.05	3.06
28	76.01	75.97	6.93	6.92	3.85	3.82
29	68.65	68.56	6.55	6.46	7.28	6.94
30	82.44	82.28	7.26	7.32	4.81	4.74
31	70.92	70.58	6.45	6.44	6.89	6.68
32	68.65	68.29	6.55	6.25	7.28	7.19
33	76.21	75.97	7.23	7.34	7.73	7.80
34	73.38	73.29	6.43	6.41	7.44	7.39

very good selectivity ratio (304). Conversion of this primary amine to secondary (**32**) and then to tertiary (**33**) induces a gradual and slight loss of MT_2 affinity (0.51 and 0.94, respectively) and selectivity (MT_1/MT_2 ratio: 162 and 53, respectively). By contrast, replacement of the amine group (**32**) by carbamate (**31**) or acetamide (**34**) gives derivatives of low and comparable MT_1/MT_2 selectivity ratios (15 and 5, respectively) resulting from a 10-fold loss of MT_2 binding affinity with a parallel increase of MT_1, particularly in the case of the acetamido compound.

3. Conclusion

The data highlight the role of the phenyl group located in the C-3 position of the naphthalene nucleus and confirm the presence of a hydrophobic pocket at the MT_2 receptor subtype. On the other hand, the MT_2 binding affinity as well as the MT_1/MT_2 selectivity ratio strongly depend on the presence, the location and the nature of functional groups on the C-3 phenyl group. Indeed the MT_2 affinities varies from 0.30 nM for **30** to over 43 nM for **19** and the selectivity ratios (MT_1/MT_2) from 5 for **34** to over 763 for **21**. This suggests the decisive intervention of some other parameters related to these functionalities.

4. Experimental

4.1. Chemistry

Melting points were determined on a Buchi SMP-20 capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 297 or a Vector 22 Bruker spectrometer. ^{1}H NMR spectra were recorded on an AC 300 Bruker spectrometer. Chemical shifts are reported in δ units (parts per million) relative to $(CH_3)_4Si$. Elemental analyses for new compounds were performed by CNRS Laboratories (Vernaison, France) (see Table 3). Obtained results were within 0.4% of the theoretical values.

4.2. General procedure for the synthesis of 3-bromo compounds (5–8)

The method adopted for the synthesis of *N*-[2-(3-bromo-7-methoxynaphth-1-yl)ethyl] acetamide (**5**) is described. To a solution of **1** (2 g, 8.22 mmol) in glacial acetic acid (40 mL) heated to 70 °C was added dropwise a solution of bromine (1.6 mL, 9.92 mmol) in 6 mL of glacial acetic acid. The mixture was stirred for 6 h at this temperature, poured after cooling into ice–water and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was recrystallized from toluene to give 1.9 g (73%) of pure **5**: mp 104–106 °C; IR (neat, cm^{-1}) 3293, 1633; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.83 (s, 3H), 3.12 (t, J = 8.3 Hz, 2H), 3.33 (m, 2H), 3.94 (s, 3H), 7.22 (dd, J = 9.0 and 2.4 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.63 (d, J = 2.4 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 8.14 (br s, 1H).

4.2.1. *N*-[2-(3-Bromo-7-methoxynaphth-1-yl)ethyl] propionamide (6)

Recrystallized from ethanol; yield 89%; mp 146–148 °C; IR (neat, cm^{-1}) 3421, 1642; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.00 (t, J = 7.6 Hz, 3H), 2.07 (qu, J = 7.6 Hz, 2H), 3.13 (m, 2H), 3.33 (m, 2H), 3.94 (s, 3H), 7.23 (dd, J = 8.8 and 2.0 Hz, 1H), 7.44 (s, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.97–8.06 (m, 2H).

4.2.2. *N*-[2-(3-Bromo-7-methoxynaphth-1-yl)ethyl]butyramide (7)

Recrystallized from ethanol; yield 48%; mp 86–88 °C; IR (neat, cm^{-1}) 3234, 1637; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.84 (t, J = 7.4 Hz, 3H), 1.51 (m, 2H), 2.04 (t, J = 7.4 Hz, 2H), 3.13 (m, 2H), 3.35 (m, 2H), 3.95 (s, 3H), 7.23 (dd, J = 9.0 and 2.5 Hz, 1H), 7.44 (d, J = 2.1 Hz, 1H), 7.60 (d, J = 2.5 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 8.00 (d, J = 2.1 Hz, 1H), 8.04 (br s, 1H).

4.2.3. *N*-[2-(3-Bromo-7-methoxynaphth-1-yl)ethyl]cyclobutyl carboxamide (8)

Recrystallized from ethanol; yield 62%; mp 154–155 °C; IR (neat, cm^{-1}) 3253, 1616; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.68–2.17 (m, 6H), 2.96 (m, 1H), 3.12 (m, 2H), 3.34 (m, 2H), 3.94 (s, 3H), 7.23 (dd, J = 8.9 and 2.1 Hz, 1H), 7.41 (d, J = 1.6 Hz, 1H), 7.57 (d, J = 2.1 Hz, 1H), 7.83 (d, J = 8.9 Hz, 1H), 7.87 (br s, 1H), 7.99 (d, J = 1.6 Hz, 1H).

4.3. General procedure for the synthesis of the 3-phenyl derivatives (9–18)

4.3.1. Method A

The method adopted for the synthesis of *N*-[2-(3-phenyl-7-methoxynaphth-1-yl)ethyl] acetamide (**9**) is described. Under N_2, a solution of **5** (1.2 g, 3.7 mmol), phenylboronic acid (0.5 g, 4.0 mmol), palladium acetate (30 mg) potassium carbonate (1.0 g, 7.3 mmol) and tetrabutylammonium bromide (20 mg) in 20 mL of dioxane and 10 mL of water was stirred at 80 °C for 4 h. After cooling and filtration, the filtrate was dissolved in ethyl acetate and washed with brine. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was recrystallized from toluene to give 0.85 g (71%) of pure **9**: mp 127–129 °C; IR (neat, cm^{-1}) 3250, 1632; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.84 (s, 3H), 3.21 (t, J = 7.5 Hz, 2H), 3.38 (m, 2H), 3.97 (s, 3H), 7.21 (dd, J = 9.0 and 2.0 Hz, 1H), 7.38 (t, J = 7.3 Hz, 1H), 7.50 (t, J = 7.3 Hz, 2H), 7.61 (d, J = 7.3 Hz, 2H), 7.78 (d, J = 2.0 Hz, 1H), 7.81 (s, 1H), 7.93 (d, J = 9.0 Hz, 1H), 8.03 (s, 1H), 8.17 (br s, 1H). Anal. ($C_{21}H_{21}NO_2$) C, H, N.

4.3.2. Method B

The method adopted for the synthesis of *N*-[2-(3-(2-formylphenyl)-7-methoxynaphth-1-yl)ethyl] acetamide (**12**) is described. Tetrakis(triphenylphosphine)palladium (0) (0.2 g) was added under N_2 to a stirred solution of **5** (2 g, 6.2 mmol) in 30 mL of toluene. After 10 min, a solution of sodium carbonate (2.9 g, 27 mmol) in 10 mL of water, then a solution of 3-formylphenylboronic acid (1.02 g, 6.8 mmol) in 6 mL of ethanol were added and the mixture was refluxed overnight. After cooling, the mixture was filtered and the filtrate was diluted with 50 mL of ethyl acetate and 50 mL of water. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The oily residue was purified by column chromatography (SiO_2, acetone/cyclohexane (2:8)) to give 2.15 g (61%) of pure **12**: oil; IR (neat, cm^{-1}) 3420, 1686, 1653; ^1H NMR (300 MHz, DMSO-d_6) δ 1.83 (s, 3H), 3.21 (m, 2H), 3.39 (m, 2H), 3.98 (s, 3H), 7.26 (dd, J = 9.1 and 1.2 Hz, 1H), 7.44 (d, J = 1.2 Hz, 1H), 7.58–7.66 (m, 2H), 7.69 (s, 2H), 7.79 (d, J = 7.6 Hz, 1H), 7.82 (s, 1H), 7.94–7.99 (m, 2H), 8.13 (br s, 1H), 9.95 (s, 1H).

4.3.3. 3-[4-(2-Acetylaminoethyl)-6-methoxynaphth-2-yl] benzoic acid methyl ester (10)

Method A: recrystallized from ethanol; yield 65%; mp 148–150 °C; IR (neat, cm^{-1}) 3369, 1724, 1661; ^1H NMR (300 MHz, DMSO-d_6) δ 1.86 (s, 3H), 3.23 (m, 2H), 3.40 (m, 2H), 3.92 (s, 3H), 3.98 (s, 3H), 7.22 (dd, J = 9.0 and 2.5 Hz, 1H), 7.62–7.71 (m, 3H), 7.94–7.99 (m, 2H), 8.05–8.10 (m, 2H), 8.17 (br s, 1H), 8.32 (s, 1H). Anal. ($C_{23}H_{23}NO_4$) C, H, N.

4.3.4. 4-[4-(2-Acetylaminoethyl)-6-methoxynaphth-2-yl] benzoic acid methyl ester (11)

Method A: purified by column chromatography (SiO_2, acetone/cyclohexane (3:7)) and recrystallized from ethanol; yield 52%; mp 147–149 °C; IR (neat, cm^{-1}) 3429, 1712, 1672; ^1H NMR (300 MHz, DMSO-d_6) δ 1.84 (s, 3H), 3.22 (m, 2H), 3.35 (m, 2H), 3.91 (s, 3H), 3.98 (s, 3H), 7.23 (d, J = 9.0 Hz, 1H), 7.67 (s, 1H), 7.75 (s, 1H), 7.92–8.23 (m, 7H). Anal. ($C_{23}H_{23}NO_4$) C, H, N.

4.3.5. *N*-[2-(3-(3-Formylphenyl)-7-methoxynaphth-1-yl)ethyl] acetamide (13)

Method B: purified by column chromatography (SiO_2, acetone/cyclohexane (3:7)) and recrystallized from ethanol; yield 68%; mp 123–125 °C; IR (neat, cm^{-1}) 3390, 1694, 1666; ^1H NMR (300 MHz, DMSO-d_6) δ 1.86 (s, 3H), 3.23 (m, 2H), 3.40 (m, 2H), 3.98 (s, 3H), 7.24 (dd, J = 9.1 and 2.4 Hz, 1H), 7.68 (d, J = 2.4 Hz, 1H), 7.74 (t, J = 7.5 Hz, 1H), 7.77 (s, 1H), 7.92 (d, J = 7.5 Hz, 1H), 7.97 (d, J = 9.1 Hz, 1H), 8.15–8.20 (m, 3H), 8.34 (s, 1H), 9.95 (s, 1H). Anal. ($C_{22}H_{21}NO_3$) C, H, N.

4.3.6. *N*-[2-(3-(3-Cyanophenyl)-7-methoxynaphth-1-yl) ethyl]acetamide (14)

Method A: recrystallized from ethanol; yield 58%; mp 141–143 °C; IR (neat, cm^{-1}) 3300, 2260, 1640; ^1H NMR (300 MHz, DMSO-d_6) δ 1.86 (s, 3H), 3.23 (m, 2H), 3.38 (m, 2H), 3.99 (s, 3H), 7.24 (d, J = 8.7 Hz, 1H), 7.68 (s, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.77 (s, 1H), 7.83 (d, J = 7.1 Hz, 1H), 7.93 (d, J = 8.7 Hz, 1H), 8.12–8.23 (m, 3H), 8.30 (s, 1H). Anal. ($C_{22}H_{20}N_2O_2$) C, H, N.

4.3.7. *N*-[2-(3-(3-Nitrophenyl)-7-methoxynaphth-1-yl) ethyl]acetamide (15)

Method A: recrystallized from ethanol; yield 87%; mp 142–144 °C; IR (neat, cm^{-1}) 3306, 1633; ^1H NMR (300 MHz, DMSO-d_6) δ 1.85 (s, 3H), 3.23 (m, 2H), 3.40 (m, 2H), 3.98 (s, 3H), 7.24 (dd, J = 8.7 and 2.6 Hz, 1H), 7.68 (d, J = 2.6 Hz, 1H), 7.77–7.83 (m, 2H), 7.98 (d, J = 8.7 Hz, 1H), 8.18 (br s, 1H), 8.21–8.25 (m, 2H), 8.29 (d, J = 7.7 Hz, 1H), 8.58 (s, 1H). Anal. ($C_{21}H_{20}N_2O_4$) C, H, N.

4.3.8. 3-[4-(2-Propionylaminoethyl)-6-methoxynaphth-2-yl] benzoic acid methyl ester (16)

Method A: recrystallized from ethanol; yield 73%; mp 113–115 °C; IR (neat, cm^{-1}) 3364, 1722, 1665; ^1H NMR (300 MHz, DMSO-d_6) δ 1.00 (t, J = 7.6 Hz, 3H), 2.10 (qu, J = 7.6 Hz, 2H), 3.23 (m, 2H), 3.41 (m, 2H), 3.92 (s, 3H), 3.98 (s, 3H), 7.23 (dd, J = 8.7 and 2.2 Hz, 1H), 7.62–7.71 (m, 3H), 7.94–8.00 (m, 2H), 8.02–8.12 (m, 3H), 8.32 (s, 1H). Anal. ($C_{24}H_{25}NO_4$) C, H, N.

4.3.9. 3-[4-(2-Butyrylaminoethyl)-6-methoxynaphth-2-yl] benzoic acid methyl ester (17)

Method A: recrystallized from ethanol; yield 52%; mp 86–88 °C; IR (neat, cm^{-1}) 3371, 1722, 1663; ^1H NMR (300 MHz, DMSO-d_6) δ 0.81 (t, J = 7.4 Hz, 3H), 1.50 (m, 2H), 2.06 (t, J = 7.4 Hz, 2H), 3.23 (m, 2H), 3.42 (m, 2H), 3.92 (s, 3H), 3.98 (s, 3H), 7.23 (dd, J = 9.0 and 2.3 Hz, 1H), 7.62–7.71 (m, 3H), 7.95–7.99 (m, 2H), 8.03–8.11 (m, 3H), 8.32 (s, 1H). Anal. ($C_{25}H_{27}NO_4$) C, H, N.

4.3.10. 3-[4-(2-Cyclobutylcarbonylaminoethyl)-6-methoxynaphth-2-yl]benzoic acid methyl ester (18)

Method A: recrystallized from ethanol; yield 43%; mp 128–130 °C; IR (neat, cm^{-1}) 3299, 1720, 1635; ^1H NMR (300 MHz, DMSO-d_6) δ 1.66–2.17 (m, 6H), 2.99 (m, 1H), 3.23 (m, 2H), 3.42 (m, 2H), 3.92 (s, 3H), 3.98 (s, 3H), 7.24 (dd, J = 8.6 and 2.0 Hz, 1H), 7.61 (d, J = 2.1 Hz, 1H), 7.63–7.69 (m, 2H), 7.91 (br s, 1H), 7.95–7.99 (m, 2H), 8.08 (d, J = 7.8 Hz, 1H), 8.11 (d, J = 1.5 Hz, 1H), 8.32 (s, 1H). Anal. ($C_{26}H_{27}NO_4$) C, H, N.

4.3.11. 3-(4-(2-Acetylaminoethyl)-6-methoxynaphth-2-yl) benzoic acid (19)

To a solution of **10** (1.5 g, 3.97 mmol) in 50 mL of methanol was added 10 mL of an aqueous solution of NaOH (0.5 g, 11.91 mmol). The mixture was refluxed for 2 h, poured into 100 mL of water and then extracted twice with ether. The aqueous layer was acidified with 10 mL of concentrated HCl and the resulting precipitate was filtered, washed with water, then recrystallized from ethanol to give 1.24 g (86%) of pure **19**: mp 221–223 °C; IR (neat, cm^{-1}) 3500–3400, 3275, 1677, 1638; ^1H NMR (300 MHz, DMSO-d_6) δ 1.86 (s, 3H), 3.22 (m, 2H), 3.41 (m, 2H), 3.99 (s, 3H), 7.23 (dd, J = 9.0 and 2.6 Hz, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.66 (s, 1H), 7.71 (s, 1H), 7.93–8.00 (m, 2H), 8.06 (dd, J = 7.9 and 1.6 Hz, 1H), 8.10 (s, 1H), 8.17 (br s, 1H), 8.33 (d, J = 1.6 Hz, 1H), 13.14 (br s, 1H). Anal. ($C_{22}H_{21}NO_4$) C, H, N.

4.4. General procedure for the synthesis of the 3-(hydroxymethyl)phenyl compounds (20–25)

4.4.1. Method 1

The method adopted for the synthesis of *N*-[2-(3-(3-hydroxymethylphenyl)-7-methoxynaphth-1-yl)ethyl] acetamide (**21**) is described. A solution of **10** (2.1 g, 5.5 mmol) in 30 mL of ether and 10 mL of THF was cooled to −5 °C and then lithium aluminum hydride (0.6 g, 16.5 mmol) was added portionwise. The mixture was stirred at room temperature for 6 h, then excess of lithium aluminum hydride was hydrolyzed with an aqueous solution of NaOH 20%. The resulting precipitate was filtered, washed with THF and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, acetone/cyclohexane (3:7)) and recrystallized from ethanol to give 1.92 g (72%) of pure **21**.

4.4.2. Method 2

The method adopted for the synthesis of compound **21** is described. To a solution of **13** (1 g, 2.9 mmol) in 40 mL of methanol was added portionwise sodium borohydride (0.08 g, 5.8 mmol). The mixture was stirred at room temperature for 10 min and con-

centrated under reduced pressure. The residue was taken off with ethyl acetate and the organic layer was washed with an aqueous solution of 1 N HCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a crude residue, which was recrystallized from ethanol to give 2.03 g (76%) of pure **21**: mp 153–155 °C; IR (neat, cm^{-1}) 3500–3400, 3294, 1625; ^1H NMR (300 MHz, DMSO-d_6) δ 1.86 (s, 3H), 3.23 (m, 2H), 3.41 (m, 2H), 3.98 (s, 3H), 4.62 (d, J = 5.6 Hz, 2H), 5.30 (t, J = 5.6 Hz, 1H), 7.21 (dd, J = 8.8 and 2.0 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.62–7.70 (m, 3H), 7.75 (s, 1H), 7.93 (d, J = 8.8 Hz, 1H), 8.03 (s, 1H), 8.17 (br s, 1H). Anal. ($C_{22}H_{23}NO_3$) C, H, N.

4.4.3. *N*-[2-(3-(2-Hydroxymethylphenyl)-7-methoxynaphth-1-yl)ethyl]acetamide (20)

Method B: recrystallized from cyclohexane; yield 92%; mp 57–59 °C; IR (neat, cm^{-1}) 3500–3250, 1636; ^1H NMR (300 MHz, DMSO-d_6) δ 1.86 (s, 3H), 3.17 (m, 2H), 3.39 (m, 2H), 3.99 (s, 3H), 4.47 (s, 2H), 5.15 (br s, 1H), 7.21 (dd, J = 8.8 and 2.6 Hz, 1H), 7.29–7.46 (m, 3H), 7.58–7.67 (m, 2H), 7.72 (s, 1H), 7.87 (d, J = 8.8 Hz, 1H), 8.16 (br s, 1H). Anal. ($C_{22}H_{23}NO_3$) C, H, N.

4.4.4. *N*-[2-(3-(4-Hydroxymethylphenyl)-7-methoxynaphth-1-yl)ethyl]acetamide (22)

Method A: recrystallized from ethanol; yield 52%; mp 164–166 °C; IR (neat, cm^{-1}) 3400–3200, 1645; ^1H NMR (300 MHz, DMSO-d_6) δ 1.86 (s, 3H), 3.20 (m, 2H), 3.38 (m, 2H), 3.97 (s, 3H), 4.56 (d, J = 5.7 Hz, 2H), 5.26 (t, J = 5.7 Hz, 1H), 7.20 (dd, J = 8.9 and 2.3 Hz, 1H), 7.44 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 2.3 Hz, 1H), 7.68 (d, J = 1.8 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.91 (d, J = 8.9 Hz, 1H), 8.03 (d, J = 1.8 Hz, 1H), 8.17 (br s, 1H). Anal. ($C_{22}H_{23}NO_3$) C, H, N.

4.4.5. *N*-[2-(3-(3-Hydroxymethylphenyl)-7-methoxynaphth-1-yl)ethyl]propionamide (23)

Method A: recrystallized from ethanol; yield 72%; mp 135–137 °C; IR (neat, cm^{-1}) 3300–3200, 1627; ^1H NMR (300 MHz, DMSO-d_6) δ 1.00 (t, J = 7.6 Hz, 3H), 2.10 (qu, J = 7.6 Hz, 2H), 3.21 (m, 2H), 3.41 (m, 2H), 3.98 (s, 3H), 4.60 (d, J = 5.6 Hz, 2H), 5.29 (t, J = 5.6 Hz, 1H), 7.21 (d, J = 8.7 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.59–7.68 (m, 3H), 7.74 (s, 1H), 7.93 (d, J = 8.7 Hz, 1H), 8.00–8.10 (m, 2H). Anal. ($C_{23}H_{25}NO_3$) C, H, N.

4.4.6. *N*-[2-(3-(3-Hydroxymethylphenyl)-7-methoxynaphth-1-yl)ethyl]butyramide (24)

Method A: recrystallized from ethanol; yield 25%; mp 113–115 °C; IR (neat, cm^{-1}) 3300–3200, 1626; ^1H NMR (300 MHz, DMSO-d_6) δ 0.83 (t, J = 7.5 Hz, 3H), 1.51 (m, 2H), 2.06 (t, J = 7.5 Hz, 2H), 3.21 (m, 2H), 3.41 (m, 2H), 3.98 (s, 3H), 4.60 (s, 2H), 5.28 (br s, 1H), 7.21 (dd, J = 8.9 and 2.2 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.59–7.68 (m, 3H), 7.73 (s, 1H), 7.93 (d, J = 8.9 Hz, 1H), 8.03 (s, 1H), 8.07 (t, J = 5.5 Hz, 1H). Anal. ($C_{24}H_{27}NO_3$) C, H, N.

4.4.7. *N*-[2-(3-(3-Hydroxymethylphenyl)-7-methoxynaphth-1-yl)ethyl]cyclobutyl carboxamide (25)

Method A: recrystallized from ethanol; yield 40%; mp 131–133 °C; IR (neat, cm^{-1}) 3300–3200, 1627; ^1H NMR (300 MHz, DMSO-d_6) δ 1.67–2.18 (m, 6H), 2.99 (m, 1H), 3.19 (m, 2H), 3.40 (m, 2H), 3.98 (s, 3H), 4.61 (s, 2H), 5.27 (br s, 1H), 7.22 (dd, J = 9.0 and 2.1 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.63–7.68 (m, 2H), 7.73 (s, 1H), 7.89–7.96 (m, 2H), 8.03 (br s, 1H). Anal. ($C_{25}H_{27}NO_3$) C, H, N.

4.4.8. *N*-[2-(3-(3-Bromomethylphenyl)-7-methoxynaphth-1-yl) ethyl]acetamide (26)

To a solution of **21** (0.6 g, 1.7 mmol) in 10 mL of glacial acetic acid was added a solution of 45% HBr in acetic acid (3.1 mL, 17 mmol). After stirring for 1 day at room temperature, the mixture was poured into water, the resulting precipitate was filtered, washed with water and recrystallized from ethanol; yield 55%; mp 118–120 °C; IR (neat, cm^{-1}) 3261, 1626; ^1H NMR (300 MHz, DMSO-d_6) δ 1.86 (s, 3H), 3.21 (m, 2H), 3.37 (m, 2H), 3.98 (s, 3H), 4.83 (s, 2H), 7.22 (dd, J = 8.9 and 2.4 Hz, 1H), 7.44–7.52 (m, 2 H), 7.66 (d, J = 2.4 Hz, 1H), 7.68 (d, J = 1.6 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.89 (s, 1H), 7.94 (d, J = 8.9 Hz, 1H), 8.06 (s, 1H), 8.17 (br s, 1H). Anal. ($C_{22}H_{22}BrNO_2$) C, H, N.

4.4.9. *N*-[2-(3-(3-Iodomethylphenyl)-7-methoxynaphth-1-yl) ethyl]acetamide (27)

To a solution of **26** (0.35 g, 0.85 mmol) in 20 mL of acetone was added sodium iodide (0.14 g, 0.94 mmol). The mixture was refluxed for 2 h. After cooling and filtration, the filtrate was concentrated under reduced pressure to afford a crude residue, which was recrystallized from toluene; yield 60%; mp 155–157 °C; IR (neat, cm^{-1}) 3263, 1635; ^1H NMR (300 MHz, DMSO-d_6) δ 1.85 (s, 3H), 3.21 (m, 2H), 3.37 (m, 2H), 3.98 (s, 3H), 4.73 (s, 2H), 7.22 (dd, J = 8.9 and 2.4 Hz, 1H), 7.44–7.46 (m, 2H), 7.63–7.71 (m, 3H), 7.88 (s, 1H), 7.94 (d, J = 8.9 Hz, 1H), 8.04 (s, 1H), 8.16 (br s, 1H). Anal. ($C_{22}H_{22}INO_2$) C, H, N.

4.4.10. *N*-[2-(3-(3-Methoxymethylphenyl)-7-methoxynaphth-1-yl)ethyl]acetamide (28)

To a solution of **26** (0.1 g, 0.24 mmol) in 2 mL of methanol was added dropwise sodium methoxide (0.026 g, 0.48 mmol) in 10 mL of methanol. The mixture was refluxed for 4 h and progressively allowed to cool to room temperature, then concentrated under reduced pressure. The residue was taken off with ether and washed with water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford a crude residue, which was recrystallized from ethanol; yield 75%; mp 86–87 °C; IR (neat, cm^{-1}) 3267, 1635; ^1H NMR (300 MHz, DMSO-d_6) δ 1.86 (s, 3H), 3.21 (m, 2H), 3.30 (s, 3H), 3.37 (m, 2H), 3.97 (s, 3H), 4.52 (s, 2H), 7.21 (dd, J = 8.9 and 2.4 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.65 (d, J = 2.4 Hz, 1H), 7.68 (d, J = 1.8 Hz, 1H), 7.70–7.74 (m, 2H), 7.94 (d, J = 8.9 Hz, 1H), 8.04 (d, J = 1.6 Hz, 1H), 8.16 (br s, 1H). Anal. ($C_{23}H_{25}NO_3$) C, H, N.

4.4.11. *N*-[2-(3-(3-Aminomethylphenyl)-7-methoxynaphth-1-yl)ethyl]acetamide hydrochloride (29)

An NH_3-oversaturated solution of **14** (1.2 g, 3.5 mmol) in 100 mL of methanol was hydrogenated over Raney nickel under pressure (50 bar) at 60 °C for 12 h. After filtration and evaporation, the oily residue was dissolved in dry ether and treated with gaseous HCl. The precipitate was filtered and recrystallized from isopropanol to give 0.43 g (32%) of pure **29**: mp 239–241 °C; IR (neat, cm^{-1}) 3425–3200, 3258, 1624; ^1H NMR (300 MHz, DMSO-d_6) δ 1.86 (s, 3H), 3.21 (m, 2H), 3.39 (m, 2H), 3.99 (s, 3H), 4.13 (m, 2H), 7.23 (dd, J = 8.8 and 2.1 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.66 (d, J = 2.1 Hz, 1H), 7.75 (d, J = 1.7 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 8.02 (d, J = 1.7 Hz, 1H), 8.09 (s, 1H), 8.29 (br s, 1H), 8.56 (br s, 3H). Anal. ($C_{22}H_{25}ClN_2O_2$) C, H, N.

4.4.12. *N*-[2-(3-(3-Aminophenyl)-7-methoxynaphth-1-yl) ethyl]acetamide hydrochloride (30)

A solution of **15** (3 g, 8.2 mmol) in 100 mL of methanol was hydrogenated over 10% Pd/C (0.1 g) at atmospheric pressure for 6 h. After filtration and evaporation, the oily residue was dissolved in dry ether and treated with HCl gas. The precipitate was filtered and recrystallized from 1-propanol; yield 79%; mp 259–261 °C; IR (neat, cm^{-1}) 3253, 3100–2700, 1612; ^1H NMR (300 MHz, DMSO-d_6) δ 1.84 (s, 3H), 3.21 (m, 2H), 3.38 (m, 2H), 3.97 (s, 3H), 7.24 (dd, J = 9.0 and 2.3 Hz, 1H), 7.34 (dd, J = 7.8 and 1.3 Hz, 1H), 7.58

(t, J = 7.8 Hz, 1H), 7.60–7.66 (m, 3H), 7.71 (br s, 3H), 7.78 (dd, J = 7.8 and 1.3 Hz, 1H), 7.94 (d, J = 9.0 Hz, 1H), 8.01 (d, J = 1.9 Hz, 1H), 8.21 (br s, 1H). Anal. ($C_{21}H_{23}ClN_2O_2$) C, H, N.

4.4.13. *N*-[2-(3-(3-Ethoxycarbonylaminophenyl)-7-methoxynaphth-1-yl)ethyl]acetamide (31)

To a solution of **30** (3 g, 8.1 mmol) in 30 mL of THF was added diisopropylethylamine (4.3 mL, 24 mmol). After cooling to 0 °C, ethyl chloroformate (1.2 mL, 12 mmol) was added dropwise, then the mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. The residue was taken off with ethyl acetate and the organic layer was washed with water, 1 N HCl aqueous solution and then with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a crude residue, which was recrystallized from ethanol to give 2.3 g (70%) of pure **31**: mp 155–157 °C; IR (neat, cm^{-1}) 3381, 3322, 1721, 1671; ^1H NMR (300 MHz, DMSO-d_6) δ 1.27 (t, J = 7.0 Hz, 3 H), 1.86 (s, 3H), 3.20 (m, 2H), 3.41 (m, 2H), 3.98 (s, 3H), 4.16 (qu, J = 7.0 Hz, 2H), 7.21 (dd, J = 9.1 and 2.1 Hz, 1H), 7.37–7.41 (m, 2H), 7.44 (m, 1H), 7.59 (d, J = 1.6 Hz, 1H), 7.65 (d, J = 2.1 Hz, 1H), 7.90–7.95 (m, 3H), 8.17 (br s, 1H), 9.74 (br s, 1H). Anal. ($C_{24}H_{26}N_2O_4$) C, H, N.

4.4.14. *N*-[2-(3-(3-Methylaminophenyl)-7-methoxynaphth-1-yl)ethyl]acetamide hydrochloride (32)

To a solution of *N*-[2-(3-(3-aminophenyl)-7-methoxynaphth-1-yl)ethyl]acetamide (1 g, 3 mmol) in ethyl orthoformate (26 mL, 156 mmol) were added four drops of trifluoroacetic acid. The mixture was refluxed for 3 h and concentrated under reduced pressure. The residue was taken off with ether and the organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a residue which was taken off with 20 mL of ethanol. Sodium borohydride (0.17 g, 4.5 mmol) was added portionwise and the mixture was stirred at room temperature for 12 h, then refluxed for 2 h. After cooling, the mixture was concentrated under reduced and the residue was dissolved in 50 mL of methylene chloride. The organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a residue which was purified by column chromatography (SiO_2, acetone/cyclohexane (3:7)). Fractions that contained **32** were combined and concentrated under reduced pressure. The residue was dissolved in ether and treated with HCl gas. The precipitate was filtered and recrystallized from acetonitrile to give 0.53 g (46%) of pure **32**: mp 186–189 °C; IR (neat, cm^{-1}) 3500–3250, 1673; ^1H NMR (300 MHz, DMSO-d_6) δ 1.85 (s, 3H), 3.03 (s, 3H), 3.22 (m, 2H), 3.40 (m, 2H), 3.98 (s, 3H), 5.50–6.20 (br s, 2H), 7.24 (dd, J = 9.0 and 2.4 Hz, 1 H), 7.56 (d, J = 7.6 Hz, 1 H), 7.65 (t, J = 7.6 Hz, 1H), 7.67 (d, J = 2.4 Hz, 1H), 7.70 (s, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.92–7.96 (m, 2H), 8.08 (s, 1H), 8.28 (br s, 1H). Anal. ($C_{22}H_{25}ClN_2O_2$) C, H, N.

4.4.15. *N*-[2-(3-(3-Dimethylaminophenyl)-7-methoxynaphth-1-yl)ethyl]acetamide (33)

To a solution of *N*-[2-(3-(3-aminophenyl)-7-methoxynaphth-1-yl)ethyl]acetamide (0.4 g, 1.2 mmol) in 20 mL of acetonitrile were added 37% aqueous formaldehyde (0.4 mL) and sodium cyanoborohydride (0.23 g, 3.6 mmol). The mixture was stirred at room temperature for 2 h and 2 N HCl aqueous solution was added dropwise until formation of a white precipitate. Acetonitrile was removed under reduced pressure and the residue was taken off with 40 mL of ethyl acetate. The organic layer was washed with 10% aqueous potassium carbonate, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a residue, which was recrystallized from isopropylic ether to give 0.16 g (37%) of pure **33**: mp 127–130 °C; IR (neat, cm^{-1}) 3264, 1635; ^1H NMR (300 MHz, DMSO-d_6) δ 1.86 (s, 3H), 2.99 (s, 6H), 3.21 (m, 2H), 3.39 (m, 2H), 3.97 (s, 3H), 6.75 (dd, J = 8.3 and 1.9 Hz, 1H), 7.02–7.07 (m, 2H), 7.20 (dd, J = 8.9 and 2.6 Hz, 1H), 7.29 (t, J = 8.3 Hz, 1H), 7.64 (m, 2H), 7.92 (d, J = 8.9 Hz, 1H), 8.00 (s, 1H), 8.16 (br s, 1H). Anal. ($C_{23}H_{26}N_2O_2$) C, H, N.

4.4.16. *N*-[2-(3-(3-Acetylaminophenyl)-7-methoxynaphth-1-yl)ethyl]acetamide (34)

Potassium carbonate (0.36 g, 2.6 mmol) was added to a solution of **30** (0.5 g, 1.3 mmol) in 10 mL of water and 30 mL of methylene chloride. The mixture was stirred for 20 min at 0 °C and acetyl chloride (0.2 g, 2.6 mmol) was added dropwise at the same temperature. After stirring at room temperature for 2 h, the organic layer was separated, washed with water, 1 N HCl aqueous solution, and water until pH 7 was reached, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was recrystallized from ethanol/water (1:1) to give 0.34 g (67%) of pure **34**: mp 218–220 °C; IR (neat, cm^{-1}) 3341, 3276, 1683, 1650; ^1H NMR (300 MHz, DMSO-d_6) δ 1.86 (s, 3H), 2.12 (s, 3H), 3.21 (m, 2H), 3.39 (m, 2H), 3.99 (s, 3H), 7.21 (dd, J = 9.1 and 2.0 Hz, 1H), 7.38–7.47 (m, 2H), 7.61 (d, J = 1.6 Hz, 1H), 7.63 (m, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.93 (d, J = 9.1 Hz, 1H), 7.96 (s, 1H), 8.20 (s, 1H), 8.17 (br s, 1H), 10.09 (br s, 1H). Anal. ($C_{23}H_{24}N_2O_3$) C, H, N.

4.5. Pharmacology

4.5.1. Reagents and chemicals

2-[^{125}I]Iodomelatonin (2200 Ci/mmol) was purchased from NEN (Boston, MA). Other drugs and chemicals were purchased from Sigma–Aldrich (Saint Quentin, France).

4.5.2. Cell culture

HEK (provided by A.D. Strosberg, Paris, France) and CHO cell lines stably expressing the human melatonin MT_1 or MT_2 receptors were grown in DMEM medium supplemented with 10% foetal calf serum, 2 mM glutamine, 100 IU/mL penicillin and 100 μg/mL streptomycin. Grown at confluence at 37 °C (95% O_2/5% CO_2), they were harvested in PBS containing EDTA 2 mM and centrifuged at 1000g for 5 min (4 °C). The resulting pellet was suspended in Tris 5 mM (pH 7.5), containing EDTA 2 mM and homogenized using a Kinematica polytron. The homogenate was then centrifuged (95,000g, 30 min, 4 °C) and the resulting pellet suspended in 75 mM Tris (pH 7.5), 12.5 mM $MgCl_2$ and 2 mM EDTA. Aliquots of membrane preparations were stored at −80 °C until use.

4.5.3. Binding assays

2-[^{125}I]Iodomelatonin binding assay conditions were essentially as previously described.[41] Briefly, binding was initiated by addition of membrane preparations from stable transfected HEK or CHO cells diluted in binding buffer (50 mM Tris–HCl buffer, pH 7.4, containing 5 mM $MgCl_2$) to 2-[^{125}I]iodomelatonin (25 or 200 pM for MT_1 and MT_2 receptors, respectively, expressed in HEK cells or 20 pM for MT_1 and MT_2 receptors expressed in CHO cells) and the tested drug. Non-specific binding was defined in the presence of 1 μM melatonin. After a 120 min incubation at 37 °C, reaction was stopped by rapid filtration through GF/B filters presoaked in 0.5% (v/v) polyethylenimine. Filters were washed three times with 1 mL of ice-cold 50 mM Tris–HCl buffer, pH 7.4.

Data from the dose–response curves (seven concentrations in duplicate) were analysed using the program PRISM (Graph Pad Software Inc., San Diego, CA) to yield IC_{50} (inhibitory concentration 50). Results are expressed as $K_i = IC_{50}/1 + ([L]/K_D)$, where [L] is the concentration of radioligand used in the assay and K_D, the dissociation constant of the radioligand characterising the membrane preparation.

[^{35}S]GTPγS binding assay was performed according to published methodology.[41] Briefly, membranes from transfected CHO

cells expressing MT_2 receptor subtype and compounds were diluted in binding buffer (20 mM HEPES, pH 7.4, 100 mM NaCl, 3 μM GDP, 3 mM $MgCl_2$, and 20 μg/mL saponin). Incubation was started by the addition of 0.2 nM [^{35}S]GTPγS to membranes (20 μg/mL) and drugs, and further followed for 1 h at room temperature. For experiments with antagonists, membranes were preincubated with both the melatonin (3 nM) and the antagonist for 30 min prior the addition of [^{35}S]GTPγS. Non-specific binding was defined using cold GTPγS (10 μM). Reaction was stopped by rapid filtration through GF/B filters followed by three successive washes with ice-cold buffer.

Usual levels of [^{35}S]GTPγS binding (expressed in dpm) were for CHO-MT_2 membranes: 2000 for basal activity, 8000 in the presence of melatonin 1 μM and 180 in the presence of GTPγS 10 μM which defined the non-specific binding. Data from the dose–response curves (seven concentrations in duplicate) were analysed by using the program PRISM (Graph Pad Software Inc., San Diego, CA) to yield EC_{50} (effective concentration 50%) and E_{max} (maximal effect) for agonists. Antagonist potencies are expressed as $K_B = IC_{50}/1 + ([Ago]/EC_{50}$ ago), where IC_{50} is the inhibitory concentration of antagonist that gives 50% inhibition of [^{35}S]GTPγS binding in the presence of a fixed concentration of melatonin ([Ago]) and EC_{50} ago is the EC_{50} of the molecule when tested alone. I_{max} (maximal inhibitory effect) was expressed as a percentage of that observed with melatonin at 3 nM for MT_2 receptor.

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